REMARKS/ARGUMENTS

Independent claim 1 has been amended by removing the range of the antifungal in the formulation. This antifungal range has been added to dependent claim 4. Independent claim 75 has been amended to recite the specific particle size distribution of the Dey FP formulation found to provide surprising results as discussed in the Examples section of one of the parent applications (i.e., U.S. Publication No. 2004/0208830 (Ser. No. 10/414,682)). Applicant notes that the Dey FP formulation used in the Examples section of Ser. No. 10/414,682 had the same particle size distribution recited in each of the currently amended claims and contained 0.05% by weight of fluticasone. As provided in paragraph [0001] of the published application (i.e., U.S. Publication No. 2004/0209852), Publication No. 2004/0208830 (Ser. No. 10/414,682) has been incorporated by reference in its entirety. No new matter has been entered.

I. IDS

Applicant notes that the document attached to the end of this response (for ease of reference) is being submitted in an IDS filed concurrently with this response. This document is being submitted for informational purposes only. That is, the document is being submitted only to show reported particle size distributions of Flonase. Applicant notes that this document was located online. As such, the citation format for this document follows the guidelines set forth in MPEP 707.05(e)IV.

II. The Currently Claimed Invention

The currently claimed invention comprises a nasal pharmaceutical formulation for the treatment of rhinitis comprising an aqueous suspension of 0.04% to 0.06% by weight of suspended solid fluticasone having a specific suspended solid particle size distribution profile (shown to provide surprising results) characterized by 5 different micron ratings of the solid fluticasone particles in combination with an antifungal agent or an aqueous suspension of 0.04% to 0.045% by weight of suspended solid beclomethasone having a specific suspended solid particle size distribution profile (shown to provide surprising results) characterized by 5 different micron ratings of the solid beclomethasone particles in combination with an antifungal agent.

The respective particle size distributions claimed for fluticasone and beclomethasone recited in the currently pending claims have surprisingly shown to provide increased bioavailability over conventional formulations as evident by the factually reported increased magnitude of improvement in several patients (e.g., reduction in the signs and symptoms of seasonal allergic rhinitis (SAR)). That is, patients receiving the currently claimed formulations which recite the particular particle size distributions (i.e., a particular distribution for fluticasone and a particular distribution for beclomethasone) attributed to the increased magnitude of improvement realize a surprisingly increased reduction in the symptoms of SAR. As discussed in further detail below, the currently claimed formulations were compared to Flonase and Beconase. The recited particle size distributions for fluticasone and beclomethasone were the only difference from the Flonase and Beconase formulations, respectively. As discussed below, the particle size distribution of Flonase and Beconase have each been reported to be significantly different than that of the currently claimed invention.

III. Rejections under 35 U.S.C. §103

To establish a *prima facie* case of obviousness, according to a test predominately used by the courts, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

With regard to the Supreme Court's decision in *KSR Int'l. Co. v. Teleflex, Inc.*, 550 U.S. ___, 82 USPQ2d 1385 (2007), it is noted that the Court did not dismiss the usefulness the well-established "teaching, suggestion, or motivation" test set forth above, but merely cautioned against its rigid application. The Supreme Court in *KSR* commented that the Federal Circuit "no doubt has applied the test in accord with these principles [set forth in *KSR*] in many cases." *Id.* at

___, 82 USPQ2d at 1396. However, the Supreme Court also opined that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. . ." *Id.* at ___, 82 USPQ2d at 1395-96. Regardless of the precise test used, the Court, quoting *In re Kahn*, cautioned that " '[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.' " *Id.* at ___, 82 USPQ2d at 1396.

A.

Claims 1, 4-6, 10-13, 22-25, 27-30, and 35 stand rejected under 35 U.S.C. §103(a) as being obvious over "FLONASE®" from the online Physician's Desk Reference ("PDR®"), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) (hereinafter "Lacy") in view of U.S. Patent No. 6,464,958 to Bernini et al. (hereinafter "Bernini"), WO 99/18971 to Harris (hereinafter "Harris"), and U.S. Publication No. 2002/0061281 to Osbakken et al. (hereinafter "Osbakken"). The Office has indicated that Harris is provided merely as a supporting reference to demonstrate particle sizes recognized in the art.

Applicant submits that each of Flonase, Bernini, Osbakken, and Harris fail to teach, suggest, or render predictable each and every element as recited in independent claims 1, 35, and 75 or any claims dependent thereon. Specifically, none of the cited references teach, suggest, or render predictable any of the following: (1) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results and (2) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited in independent claims 1, 35, and 75.

Flonase is a 50 mcg of microcrystalline aqueous suspension of fluticasone propioinate,. Flonase can be used for the perennial rhinitis in patients above 12 years of age. A controlled study was performed where the fluticasone used in the Dey FP nasal spray was derived from a different source than Flonase (i.e. the Dey FP nasal spray had a different particle size distribution

then Flonase). For instance, the particle size distribution of Flonase has been reported in a white paper by ChemImage (hereinafter "ChemImage") to be significantly different than the distribution recited in the currently claimed invention. ChemImage is provided at the end of this response and is also being submitted in an IDS being filed concurrently with the present response. Figure 1 of ChemImage shows the Raman dispersive spectra of Flonase and Figure 3 lists the particle size of Flonase (i.e., innovator) as follows: (i) D10 = 1.0 microns; (ii) D50 = 4.7 microns; and (iii) D90 = 13.5 microns. That is, ChemImage shows that the particle size distribution of Flonase has the following distribution:

Flonase PSD as reported by ChemImage

D10	D50	D90
1.0	4.7	13.5

For comparison, the currently claimed invention recites, the following particle size distribution:

Claimed PSD

D10	D50	D90
0.4	1.5	5.3

Upon comparison of the reported particle size distribution of Flonase with the currently claimed distributions, it is readily apparent that the particle size distribution of Flonase generally contains larger particles and a wider distribution of particles. For instance, about 50% of the particles in Flonase are greater than 4.7 microns. To the contrary, the currently claimed invention recites that about 90% of the fluticasone particles are less than 5.3 microns. Furthermore, the reported D50 level for Flonase is roughly 3 times larger than that of the currently claimed distribution (i.e., 4.7 microns as compared to the currently recited 1.5 micron rating recited in independent claims 1, 11, and 23). Additionally, one skilled in the art would have no rational basis for modifying Flonase to have the particular particle size distribution recited in each of the currently pending independent claims. Such a modification would require a substantial alteration of the Flonase particle size distribution.

Bernini is primarily directed to a process for preparing aqueous suspensions of drug particles for inhalation into the lungs. Bernini's process includes the following steps: (i)

preparing an aqueous solution constituting the carrier and optionally containing wetting agents, surfactants, viscosity-increasing agents, stabilizing agents, isotonicity agents and/or buffers, in a suitable turboemulsifier vessel; (ii) sterilizing the aqueous base inside the same container; (iii) adding, in a sterile environment, one or more active sterile micronised ingredients (i.e. fluticasone dipropionate); and (iv) dispersing all of the ingredients by using the sameturboemulsifier. The resulting aqueous suspensions are intended for nebulisation so that the beclomethasone is deposited into the lungs.

However, each of Flonase, Bernini, and Harris fail to teach, suggest, or render predictable any of the following: (1) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results and (2) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited in independent claims 1, 35, and 75. As discussed below, Osbakken fails to cure these deficiencies.

The Office relies on Osbakken for the teaching of formulations including an antifungal agent or an antibiotic.

Osbakken is directed to compositions having a specific surface tension to yield a liquid aerosol cloud for inhalation having a mass median aerodynamic diameter (MMAD) of between 0.5 and 10 microns. Osbakken teaches adjusting the surface tension of a solution such that it yields a liquid aerosol cloud having an MMAD in a pre-determined range. For example, Osbakken teaches that "this aerosol cloud will have liquid aerosol particles" having certain MMAD ranges. Further, Osbakken stresses the importance of controlling the surface tension of the composition so that the liquid droplets are deposited in the appropriate locations of a patient. See paragraph [0092]. As noted in previous responses, Osbakken is directed to solutions of dissolved active as opposed to suspensions of solid active.

Thus, despite teaching solutions containing both an anti-inflammatory and an antifungal agent, Osbakken fails to cure all of the deficiencies noted in Flonase, Bernini, Hasrris, and any combination thereof. As such, any combination the Osbakken, Flonase, Bernini, and Harris also fails to teach, suggest, or render predictable any of the following: (1) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results

and (2) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited in independent claims 1, 35, and 75. As such, each of the cited references, alone or in any combination, fails to teach, suggest or render predictable every element currently recited in independent claims 1, 35, and 75 (or any claims dependent thereon). As such, Applicant submits that this obviousness rejection has been overcome. Applicants request withdrawal of this rejection.

B.

Claims 71-74 stand rejected under 35 U.S.C. §103(a) as being obvious over FLONASE®" from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) in view Bernini and Osbakken, and further in view of U.S. Patent No. 6,368,616 to Doi (hereinafter "Doi") and U.S. Patent No. 6,608,054 to Meade (hereinafter "Meade").

The Office relies on Doi for teaching suspensions for nasal applications containing citric acid and EDTA. The Office cites Meade for teaching that sodium edetate and citric acid are known complexing agents.

Doi is generally directed to stabilizing an aqueous suspension of loteprednol etabonate and improving intranasal retention of the active ingredients. Doi is also concerned with the feeling-of-use using thickeners including cellulose derivatives such as methylcellulose, carboxymethylcellulose sodium, hydroxypropylmethylcellulose, etc., synthetic macromolecular compounds such as polyvinyl alcohol, polyvinylpyrrolidone, carboxyvinyl polymer, etc., and saccharides such as sorbitol, mannitol, sucrose, etc.; cationic surfactants including quaternary ammonium salts; anionic surfactants including alkylsulfates; and nonionic surfactants including polysorbate 80, polyoxyethylene hydrogenated castor oil, etc.

Meade is directed to compositions including anticholinergics and endothelin antagonists that exhibit a synergistic effect in the treatment of respiratory tract diseases. Anticholinergics are a class of medications that inhibit parasympathetic nerve impulses by selectively blocking the

binding of the neurotransmitter acetylcholine to its receptor in nerve cells. Endothelin antagonists block endothelin, a 21-amino acid vasoconstricting peptide produced primarily in the endothelium. Mead teaches that such compositions can be used for the treatment of pulmonary hypertension. See column 2, line 61. The compositions may be provided in the form of a propellant-free inhalable solution or suspension, wherein the solvent may be aqueous or alcoholic. See column 8, lines 64-67.

However, neither Doi, Meade, nor any combination thereof cure the aforementioned deficiencies of Flonase, Bernini, Osbakken, or any combination thereof. As such, any combination the Osbakken, Flonase, and Bernini also fails to teach, suggest, or render predictable any of the following: (1) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results and (2) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited in independent claims 1, 35, and 75. Therefore, Doi, Meade, or any combination thereof fails to cure the deficiencies of the Flonase/Bernini or Flonase/Bernini/Osbakken. Applicant requests withdrawal of this rejection.

C.

Claims 75-76 stand rejected under 35 U.S.C. §103(a) as being obvious over FLONASE®" from the online Physician's Desk Reference ("PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Lipsy, R. J.; Lance, L.L., Lexi-Comp, Inc.: Cleveland, pp 445-446) in view Bernini and Osbakken, and further in view of "Management of Allergic Rhinitis", Nursing Times, 2003, 99(23), Abstract to Walker (hereinafter "Walker") and "Topical Antiviral Agents for Herpes Simplex Virus Infections", Drugs Today, 1998, 34(12), Abstract to Hamuy et al. (hereinafter "Hamuy").

The Office relies on Walker and Hamuy to show that viral infections are art-recognized to play a role in the etiology of rhinitis (Walker) and that cidofovir and edoxudine are will-known anti-viral agents (Hamuy).

Applicant notes, however, that none of Walker, Hamuy, or the combination of the two cures the deficiencies noted above. In particular, neither of these secondary references teach, suggest or render predictable any of the following: (1) the specifically recited particle size distribution characterized by 5 distinct levels which demonstrate surprising results and (2) an aqueous suspension of 0.04% to 0.06% by weight fluticasone having the specifically recited particle size distribution the demonstrates surprising results in combination with an antifungal agent as recited in independent claims 1, 35, and 75. Thus, Applicant requests withdrawal of this rejection.

IV. Surprising Results

A. Clarification of "high dose" / "low dose" terminology in the fluticasone study

Applicant notes that the "high dose" / "low dose" designations refer to the number of sprays including fluticasone received by patients. "Low dose" groups only received 1 spray of fluticasone per nostril in a day while "high dose" groups received 2 sprays of fluticasone per nostril over the course of a day. Thus, patients in the "low dose" groups received half the amount of fluticasone than those in the "high dose" groups.

At the outset, Applicant notes that both the Dey FP and the Flonase formulations included 50 mcg of fluticasone. However, the fluticasone used in the Dey FP nasal spray was derived from a different source from that Flonase. That is, the particle size distribution of fluticasone in the Dey FP formulation was different than that of the Flonase formulation. Other than this difference, both the Dey FP and Flonase nasal sprays contained the same excipients and additives in the same amounts. Furthermore, the Dey FP nasal spray and the Flonase spray were each administered by the same metered-dose, manual pump spray.

As referenced above, the ChemImage white paper shows that the particle size distribution of Flonase has the following distribution:

Flonase PSD as reported by ChemImage

D10	D50	D90
1.0	4.7	13.5

For comparison, the currently claimed invention recites, the following particle size distribution:

Claimed PSD

D10	D50	D90
0.4	1.5	5.3

Upon comparison of the two distributions, it is readily apparent that the particle size distribution of Flonase is substantially different than that of the currently claimed invention. For instance, Flonase clearly contains larger particles and a wider distribution of particles. For, example, about 50% of the particles in Flonase are greater than 4.7 microns. To the contrary, the currently claimed invention recites that about 90% of the fluticasone particles are less than 5.3 microns. Furthermore, the reported D50 level for Flonase is roughly 3.1 times larger than that of the currently claimed distribution (i.e., 4.7 microns as compared to the currently recited 1.5 microns).

B. Improvement in magnitude of TNSS reduction realized by patients in the Dey FP Low Dose group

The patients in the Dey FP Low Dose groups realized a superior relief of the symptoms of SAR over patients in the Flonase Low Dose group. Figure 1 provides a visual illustration of this increased relief from the symptoms of SAR. Table 1, provided below, provides an approximate quantitative value for the improved relief from the symptoms of SAR realized by patients in the Dey FP Low Dose group.

Table 1

Day	Dey FP Low Dose Group – approximate LS value	Flonase Low Dose Group – approximate LS value	% Improvement in TNSS over the Flonase Low Dose Group
7	-5.9	-4.5	**~31%**
8	-5.8	-5.1	**~14%**
9	-6.3	-5.8	**~9%**
10	-6.8	-6.2	**~10%**
11	-7.4	-5.6	**~21%**
12	-7.4	-6.1	**~19%**
13	-7.4	-6.2	**~19%**
14	-7.8	-6.5	**~20%**

Applicant submits that one skilled in the art (and one suffering from the symptoms of seasonal allergic rhinitis) would recognize the aforementioned percentages of TNSS improvement as not merely a minor difference of degree as suggested by the Office. Applicant notes that the patients in the Dey FP Low Dose group realized these improved reductions in TNSS while receiving the same amount of fluticasone than the patients in the Flonase Low Dose group. Again, the only difference in the Dey FP and Flonase formulations is the respective particle size distributions.

C. Patients in the Dey FP Low Dose group realized improved or at least similar reduction in TNSS than both High Dose groups

After about 7 days, as illustrated by Figure 1, the patients of the Dey FP Low Dose group consistently reported a reduction in TNSS better than or substantially equal to that of patients in the Flonase High Dose group. Applicant first submits that the data from the Dey FP Low Dose group shows an improvement over results realized by patients in the Flonase High Dose group. Irrespective of Applicants stance that the data or the Dey FP Low Dose group shows improvement of the Flonase High Dose group, Applicant notes that the Office's view that the data sets for the Dey FP Low Dose and the Flonase High Dose groups are essentially the same

also illustrates the surprising results realized by the currently claimed formulations (having the specifically recited particle size distribution). For instance, the patients of the Dey FP Low Dose group received half the fluticasone than the Flonase High Dose group. In view of the Office's characterization of the data sets, therefore, the Dey FP Low Dose group realized the same relief from the symptoms of SAR as the Flonase High Dose group despite receiving half the amount of fluticasone. The ability to achieve the same or similar relief from the symptoms of SAR while using half the amount of fluticasone is surprising in and of itself. That is, these results were unexpected because the skilled artisan would not have expected the Dey FP Low Dose group to realize improved relief in TNSS greater than or the same as the Flonase High Dose group (which received double the medicament).

The fact that the claimed distributions afford unexpected results provides further evidence of the non-obviousness of the currently claimed invention.

V. Double Patenting

Claim 1 stands provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending U.S. Application No. 11/931,484 in view of Lacy and Hebrecht, R. et al. "Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis" N. Eng. J. Med., 2002, 347(6), pp 408-415 (hereinafter "Hebrecht"). Applicants traverse this provisional rejection.

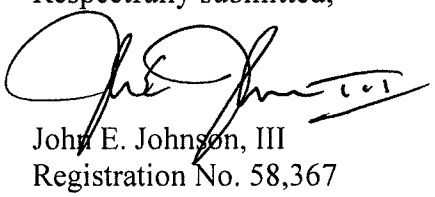
Since this is a provisional rejection and the Office has not indicated the allowance of any of the pending claims, Applicant will not file a terminal disclaimer at this time. Upon indication of allowable subject matter, Applicant will submit a terminal disclaimer to overcome the rejection.

VI. Conclusion

In view of the amendments and remarks made above, Applicant submits that the pending claims are now in condition for allowance. Applicant respectfully requests that the claims be allowed to issue. If the Examiner wishes to discuss the application or the comments herein, the Examiner is urged to contact the undersigned by telephone.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



John E. Johnson, III
Registration No. 58,367

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Charlotte Office (704) 444-1000
Fax Charlotte Office (704) 444-1111
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ChemImage™ White Paper

Comparison of Drug Particle Sizing of Innovator and Generic Nasal Spray Formulation Based on Raman Chemical Imaging

Two fluticasone propionate nasal spray formulations were characterized using Raman Chemical Imaging, for drug particle size distribution comparison between innovator and generic brands.

Measuring bioavailability (BA) and establishing bioequivalence (BE) for nasal aerosols and nasal sprays is required by U.S. Food and Drug Administration (FDA) for manufacturers in order to establish product quality in support of new drug applications (NDAs) or abbreviated new drug applications (ANDAs) (1).

For nasal spray suspension formulations, bioequivalence studies should prove that the rate and the extent at which an active pharmaceutical ingredient (API) becomes available to active sites of the nasal cavity is within the acceptance criteria established for pharmaceutical equivalence of the innovator drug product. Drug particle size distribution (PSD) is a key parameter for establishing qualitative and quantitative sameness of these products in bioequivalence (BE) studies. Drug PSD correlates with formulation product quality criteria defined by the drug particle dissolution rate. The FDA recommends providing both drug and agglomerate PSD data in the BE submission (1). It is also recommended to evaluate the effect of the actuating device on deagglomeration by determining drug PSD and degree of drug particle agglomeration in the formulation pre- and post-actuation.

The FDA has recently initiated a document describing critical path opportunities for generic drug manufacturers (2). According to the office for generic drugs, if the drug PSD of test and reference products can be demonstrated to be equivalent, then *in vivo* biostudies may be waived for nasal spray suspensions. Today, optical microscopy is the only available technique to assess *in vitro* drug particle size distribution in sprays and aerosols to support BA or BE submission for NDAs and ANDAs. Even though a qualitative and semi-quantitative estimation of drug and aggregated drug PSD can be obtained based on microscopy analysis, visual microscopy is very subjective for positive identification of suspended drug substance in the presence of insoluble suspending agents. The occurrence of apparent drug particles due to insoluble excipients in the suspensions containing placebo products has led to false positive results (1). Reliable quantitative and qualitative methods for separately measuring the PSD of specific components and aggregates in the formulation are in demand by innovators and generic manufactures alike. Ingredient-specific particle sizing (ISPS) may be very valuable for formulation development, scale-up, batch release and batch comparison studies for innovator

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companies in the market of nasal sprays, while generic manufactures could use such information to support BE studies.

Wide-field chemical imaging technology combining optical microscopy and high throughput hyperspectral Raman Chemical Imaging (3) provides a unique opportunity to obtain ingredient-specific particle sizing of the drug in aqueous suspensions (4). This article features the application of Raman Chemical Imaging (RCI) technology for comparing the drug PSD of two nasal spray formulation samples containing a corticosteroid drug from brand and generic manufacturers.

Optical microscopy, Raman dispersive spectroscopy and RCI were used to study two commercially available fluticasone propionate aqueous nasal spray samples. All data were collected using a FALCON II™ Raman Chemical Imaging Microscope (ChemImage Corporation) with 532 nm laser excitation. Actuated samples were prepared by shaking, priming (four actuations each) and spraying each nasal spray sample in an upright position onto an inverted aluminum-coated glass microscope slide positioned approximately 15 cm from the spray nozzle. The samples were then immediately turned upright and allowed to dry.

Raman spectra of all individual components of the studied formulations are presented in Figure 1. RCI experiments were set up to spectrally discriminate the drug substance (fluticasone propionate) from all excipients. The discrimination of the analyte from other ingredients in the suspension is provided by the ability to collect spatially resolved Raman spectra in the image (pixel by pixel) and the ability to discriminate a characteristic Raman band of the drug (at 1663 cm-1) (5) from Raman bands of other materials in the spectral range. ChemImage Xpert™ software was used to acquire process and analyze RCI data for determining the ISPS distribution.

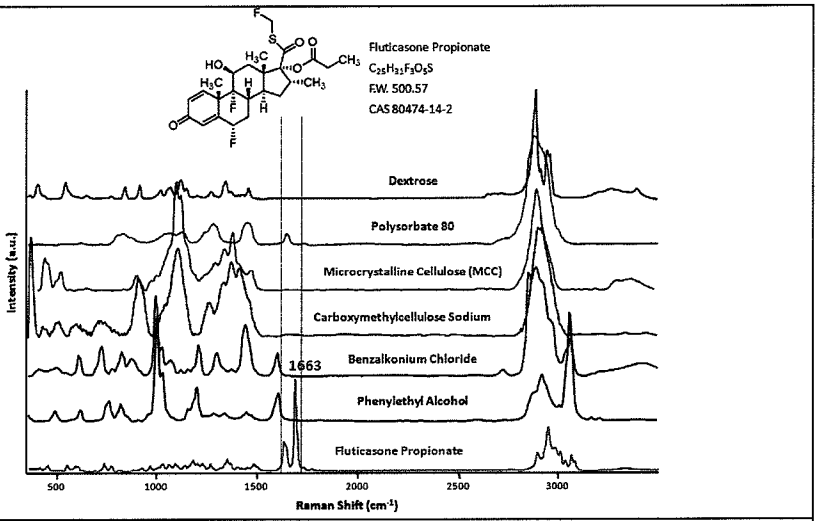


Figure 1. Raman dispersive spectra of Flonase® formulation components

Liquid Crystal Tunable Filter (LCTF) technology enables the collection of spectrally resolved imaging data in x and y dimensions of high resolution fidelity. RCI was performed on formulated generic and brand spray samples to obtain fluticasone-specific PSD for 100 particles per sample. In the current example, image contrast at the 1663 cm^{-1} Raman spectral plane can be attributed to the fluticasone propionate species (Figure 1). High intensity pixels at this wavelength are grouped with the close neighbors to spectrally define areas of the presence of fluticasone propionate within the image. A Raman Chemical Image of fluticasone propionate is superimposed or fused with an optical image of the same area to validate the binarization routine used for particle sizing. Figure 2a and 2b show representative brightfield reflectance images of both innovator and generic nasal sprays samples actuated onto a microscope slide. To achieve the desired count for drug particles per sample, a multiple field-of-view (FOV) montage was acquired. This montage is usually defined by the drug particle density approximated from a smaller subset of FOVs. A brightfield-guided image binarization (Figure 2, c, d) was then performed, and a particle size histogram for the drug substance was generated. Fusing both optical and RCI images is used to minimize the over- or underestimation of particle size compared to utilizing the RCI data alone and validate the accuracy of particle sizing.

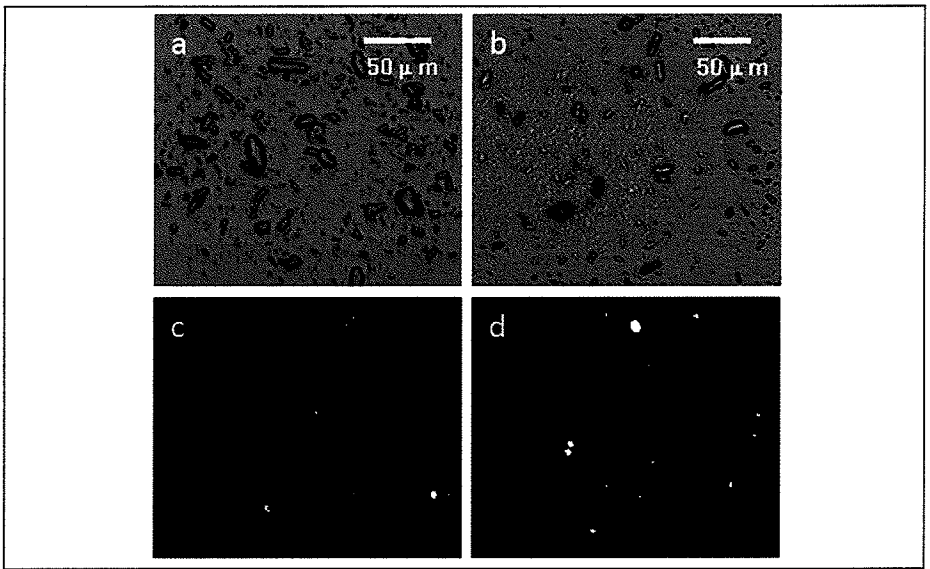
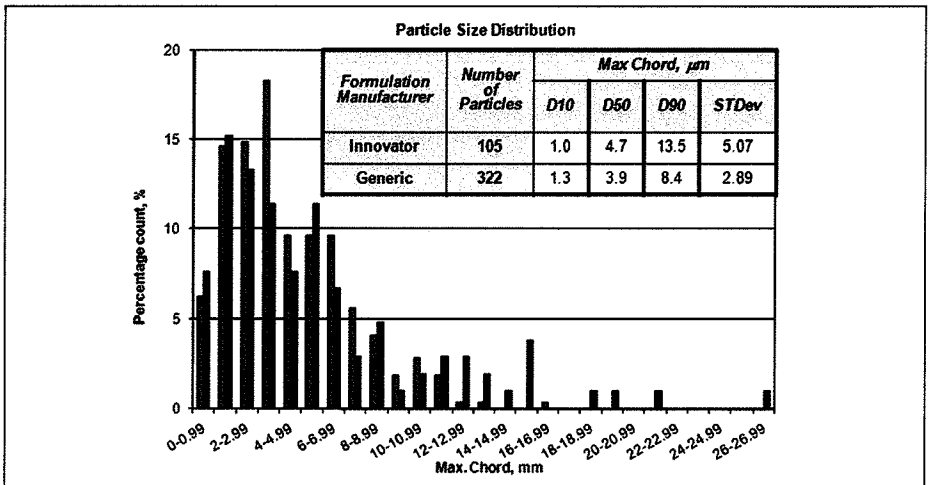


Figure 2. Representative brightfield reflectance image at 50x (a, b) and binarized chemical image of innovator (left) (c) and generic (right) (d) fluticasone propionate nasal spray samples



Formulation Manufacturer	Number of Particles	Max Chord, µm			
		D10	D50	D90	STDev
Innovator	105	1.0	4.7	13.5	5.07
Generic	322	1.3	3.9	8.4	2.89

Figure 3. Comparison of drug particle size distribution of fluticasone propionate nasal spray samples for innovator and generic manufacturers

Comparison of these two products shows that the drug particle size distribution is similar (Figure 3) but the brand product possesses larger particles and a wider distribution of sizes. Figure 4a shows an example of brightfield/RCI fusion of the identified fluticasone propionate particles in the generic fluticasone propionate formulation. Aggregates and adhered particles can be detected and sized using such fusion strategies (Figure 4 b,c). While it is required by the FDA to report drug particle agglomeration, current analytical methods do not possess this capability. Moreover, without an ability to evaluate the presence and degree of drug-excipient agglomeration sizing by conventional optical microscopy is done on pre-selected particles by the analyst. Therefore, the drug PSD is likely to be subjective and differ from the true value when microscopy is used for drug particle sizing and reporting alone. There is a great interest to advance, validate and integrate ISPS algorithms for the automated analysis of drug PSD in final formulations(6), and Raman Chemical Imaging illustrates great promise for ISPS applications for nasal drug formulation manufacturers.

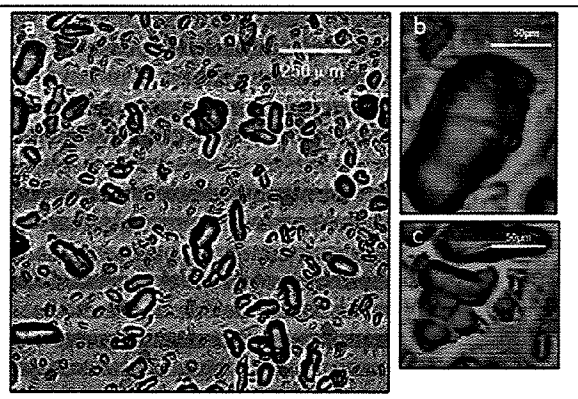


Figure 4. Brightfield reflectance image overlayed with pseudo-colored chemical image of generic fluticasone propionate nasal spray.

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1. Draft Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action. Food and Drug Administration Web site., Available at http://www.fda.gov/cder/guidance/5383DFT.pdf. Accessed on May 13, 2009.
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